Proteinuria and hypertension with tyrosine kinase inhibitors

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Tyrosine kinases are important for the development of pathological angiogenesis, a critical factor for survival and proliferation of tumor cells. Inhibition of tyrosine kinases either through targeted binding of its ligands or inhibition of its receptor has led to significant hindrance in angiogenesis and has improved survival for several cancers. Several of these antibodies or small molecules have been approved for treatment of recurrent and resistant cancers over the last decade. Although generally well tolerated, tyrosine kinase inhibitors have been linked with development of hypertension and proteinuria. We review the literature for incidence and severity of hypertension and proteinuria among several tyrosine kinase inhibitors, their pathophysiologic mechanisms, and provide a guide for screening and management.

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Tyrosine kinase inhibitors (TKIs) are a new class of antineoplastic drugs used in treatment of solid organ cancers, such as those of colon, breast, lung, and kidney among several others either alone or in combination with other chemotherapy agents. Although overall well tolerated, they are still limited in their use by significant toxicities, some of which are relevant for the practicing nephrologist. Proteinuria and hypertension have been recognized as major side effects. Although uncommon, the severity of these conditions and the rapidity of onset can be alarming. With improved survival and outcomes for cancer treatments, it is critical to identify these side effects. Management of these side effects may improve overall outcomes. The purpose of this review is to increase awareness and review the pathophysiological mechanisms of these side effects.

TYROSINE KINASE

Tyrosine kinases belong to the family of protein kinases and are classified in two broad categories: receptor tyrosine kinases (RTKs) and cytoplasmic tyrosine kinases. More than half of the 90 tyrosine kinases identified are RTKs. RTKs on binding with a ligand undergo dimerization and catalyze phosphorylation of tyrosine residues on proteins by using ATP. Such phosphorylation causes a change in the function of the cytoplasmic proteins. Several of these proteins mediate secondary effects by their action at the genetic transcription level. These can result in changes in enzyme activity, cell growth, differentiation, metabolism, adhesion, motility, and death.[1] Mutations leading to overactivity of tyrosine kinases can lead to development of cancers.[2] Accordingly, targeting RTKs or their ligands is an attractive option for treatment of many cancers.

TYROSINE KINASE INHIBITORS

Imatinib was the first TKI used to treat chronic myelogenous leukemia as it targeted the specific bcr–abl, a cytoplasmic tyrosine kinase, along with RTKs for platelet-derived growth factor receptor and c-kit. This was followed by the discovery of inhibitors to other RTKs, such as gefitinib and panitumumab for epidermal growth factor and bevacizumab and ranibizumab for vascular endothelial growth factor (VEGF). These were monoclonal antibodies directed against RTK ligands. With further improvements in drug discovery, monoclonal antibodies are being replaced by orally available

Table 1 | TKIs currently available

Name	Target receptor	Type of TKI
Bevacizumab	VEGF	Monoclonal antibody
Cetuximab	Erb1	Monoclonal antibody
Trastuzumab	Erb2	Monoclonal antibody
Ranibizumab	VEGF	Monoclonal antibody
Panitumumab	EGFR	Monoclonal antibody
Pegaptanib	VEGF	RNA aptamer
Gefitinib	EGFR	Small molecule
Imatinib	Bcr–abl	Small molecule
Sorafenib	Multiple targets	Small molecule
Dasatinib	Multiple targets	Small molecule
Sunitinib	Multiple targets	Small molecule
Erlotinib	Erb1	Small molecule
Nilotinib	Bcr–abl	Small molecule
Lapatinib	Erb1/Erb2	Small molecule
Pazopanib	VEGFR2/PDGFR/c-kit	Small molecule
Crizotinib	ALK	Small molecule

Abbreviations: ALK, anaplastic lymphoma kinase; Erb/EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

molecules that targeted RTKs directly. These molecules in addition are capable of inhibiting multiple RTKs simultaneously. Examples of orally administered RTK inhibitors include sorafenib, sunitinib, dasatinib, and pazopanib, among several others (Table 1). Recently completed phase III trials for several of these inhibitors have led to Food and Drug Administration approval for their use in treatment of several advanced cancers. These include, but are not limited to, cancers of liver (sorafenib 2007), kidney (sorafenib 2005, sunitinib 2006, and pazopanib 2009), gastrointestinal stromal tumor (sunitinib 2006), lung (erlotinib 2004), pancreas (erlotinib 2005), and chronic myelogenous leukemia (dasatinib 2010).

TKIs: mechanism of action

TKIs inhibit angiogenesis. Angiogenesis, a limited and regulated process in healthy individuals, is pivotal for survival and proliferation of tumor cells. The regulation of angiogenesis is complicated. Several growth factors such as VEGF, epidermal growth factor, and platelet-derived growth factor cause angiogenesis. Before these growth factors can cause angiogenesis, RTKs must activate them. Other regulators of angiogenesis include transcription factors such as hypoxia-inducible factor, mitogen-activated protein kinase, and phosphoinositide 3-kinase signaling.[2] Tumor cells either secrete growth factors or auto-activate RTKs through mutations, leading to a favorable proangiogenic over antiangiogenic milieu. Inhibitions through targeted actions on ligands or RTKs lead to potent antiproliferative effects by inhibiting pathological angiogenesis.

In comparison with other antineoplastic drugs, TKIs have few adverse events; two important and sometimes severe side effects of TKIs are proteinuria and hypertension.

Pathophysiology and proposed mechanisms for proteinuria with TKIs

Understanding the pathophysiology of proteinuria requires the understanding of the glomerular filtration barrier (GFB). GFB is made up of the fenestrated endothelium, glomerular basement membrane, and podocytes, which form the slit diaphragm. Together, they provide an effective barrier to prevent loss of large molecules and proteins. The foot processes of the podocytes are connected together by a slit diaphragm or membrane. The integrity of the slit diaphragm is maintained by several proteins made by the podocytes, which include nephrin, Neph1, FAT, podocin, and CD2-associated protein (CD2AP) among others. Inactivation of these protein genes in mice causes massive proteinuria, and sometimes the absence of a slit diaphragm and death.[3] Among these proteins, nephrin production has been shown to be selectively inhibited with VEGF inhibition.[4] Recent studies in genetically modified mice suggest that podocyte-derived VEGF has a major role in the development of the endothelium and the maintenance of its fenestrations. To determine the role of VEGF in development and maintenance of the GFB, Eremina *et al.*[5] generated mice with gain and loss of function specifically involving the podocytes. When VEGF gene was deleted in a homozygotic manner, mice died at birth or within 18 h with hydrops and kidney failure. When the gene was deleted in a heterozygotic manner, it resulted in renal disease by 2.5 weeks. Grossly, the kidneys appeared to be smaller and paler, and had higher creatinine and urea with lower hemoglobin. Renal biopsies revealed significant endotheliosis, defects in endothelial migration, and differentiation with loss of GFB. These findings were similar to those seen in preeclampsia. At 6.5 weeks and 9 weeks, endothelial cells became necrotic and podocyte foot processes were completely lost.[5] This confirmed the critical role of VEGF in the development of GFB. In a later study, Eremina *et al.*[6] were again able to show similar findings in selective VEGF knockout mice, confirming the role of VEGF not only in development but also in maintenance of GFB.

One may be tempted to speculate that replacement of VEGF may be of therapeutic value. However, overexpression of VEGF is also deleterious. When kidneys of mice with gain-of-function VEGF 164 expression were examined, significant surface hemorrhages were noted and renal biopsies revealed collapsing glomerulopathy as seen in HIV.[5] This similarity is interesting because HIV produces a TAT protein that signals through flk1 in the endothelial cells of Kaposi's sarcoma. Further the podocyte is a major reservoir of HIV.[7] These findings may potentially explain the pathology seen in HIV-associated collapsing focal segmental glomerulosclerosis, that is, possible VEGF overexpression.

On the basis of these findings, it is thought that VEGF produced by podocytes travels across the GFB and reaches the endothelial surfaces where it interacts with several receptors such as Flk1 (VEGF receptor 1) and Flt1 (VEGF receptor 2). This may also partly explain the proximity of the podocytes to the vascular cleft in the development of kidney. In fact, it is highly likely that VEGF may be the signal that localizes endothelial cells of the vascular cleft to the podocytes forming the glomerular basement membrane. The similarities to pathological findings in preeclampsia may

similarly be explained by increased soluble flt1.[8] As mentioned earlier, flt1 are VEGF receptors, and abnormal generation of these soluble forms of receptors by the placenta leads to binding of VEGF generated at the podocytes (as they are one of the largest VEGF-producing cells). Although administration of VEGF reversed glomerular finding in pregnant rats in this study and in experimental models of glomerulonephritis[9] and thrombotic microangiopathy (TMA),[10] Eremina *et al.*[6] did not find reversal of renal pathology in knockout mice that were made deficient in VEGF by conditional gene deletions.

Some of the other mechanisms proposed for development of proteinuria have been due to development of hypertension and the use of concomitant agents such as gemcitabine, interferon-α, and bisphosphonates, most notably pamidronate.[11] However, hypertension is unlikely to explain the development of proteinuria completely. In a study of bevacizumab in metastatic renal cell carcinoma, proteinuria only partly correlated with hypertension. A total of 54% of patients with grade 2 or 3 hypertension and 16% of patients with grade 0 or 1 developed proteinuria.[12] Although the gradation partly explains the contribution of hypertension, it does not completely explain development of proteinuria. The variable incidence of proteinuria among patients receiving TKIs highlights the possibility of differences in susceptibility for developing proteinuria, ranging from genetic make up to preexisting comorbid conditions, concomitant drugs, and type of cancer. Further studies are needed in order to understand these susceptibilities. Figure 1 demonstrates our current understanding of the pathophysiology of TKI-induced proteinuria and hypertension.

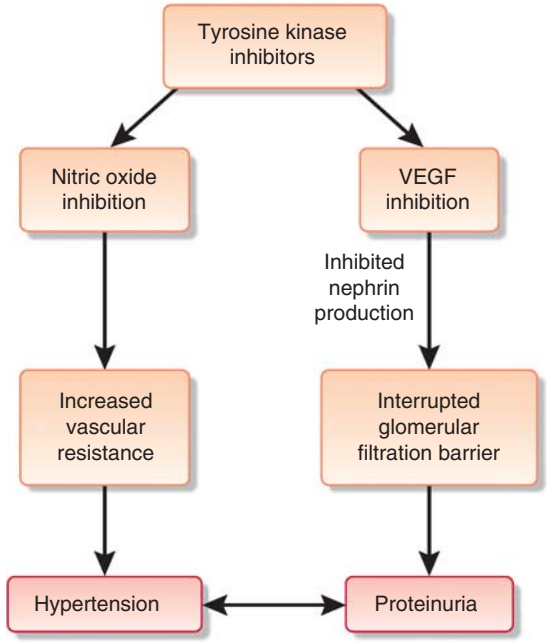

Figure 1 | Postulated mechanisms for the development of proteinuria and hypertension with tyrosine kinase inhibitors (TKIs). TKIs, by inhibiting nitric oxide production in the endothelium, increase vascular resistance and cause hypertension. By inhibiting vascular endothelial growth factor (VEGF), TKIs reduce nephrin production. Nephrin is important to maintain the integrity of the glomerular filtration barrier and its reduced production can lead to proteinuria. Renal damage can cause hypertension and hypertension can aggravate proteinuria.

Proteinuria and hypertension with TKIs

Proteinuria. Proteinuria has now been strongly linked to adverse cardiovascular outcomes and progression to end-stage renal disease in patients with chronic kidney disease.[13,14] Although the first line of management of proteinuria is to use drugs to reduce proteinuria (such as angiotensin-converting enzyme inhibitors), the more effective way to manage this condition is by treating or removing the offending condition or agent. TKIs, specifically those directed against VEGF, are associated with development of proteinuria. Proteinuria was first reported in the prototypical VEGF inhibitor—bevacizumab. A meta-analysis of seven trials involving 1850 patients revealed an increased risk of proteinuria with the use of bevacizumab. This was noted to be dose dependent (relative risk (RR) of 1.4 with low dose (95% confidence interval (CI): 1.1–1.7) and RR of 2.2 with high dose (95% CI: 1.6–2.9)). Overall incidence of proteinuria ranged from 21 to 41% in the low-dose group and 22 and 63% in high-dose group.[15] However, only 1–1.8% developed grade III proteinuria or worse. This review was limited by heterogeneity in the following characteristics that can have an important effect on proteinuria: patient populations, doses of bevacizumab, tumor types, chemotherapies, and lengths of treatment. The most important limitation of this meta-analysis was that measurement of proteinuria in some studies was based on urine dipstick testing instead of the more quantitative protein/creatinine ratio or 24-h urine collections. In a more recent follow-up review by the same authors of more than 12,000 patients, Wu *et al.*[16] identified the incidence of high-grade proteinuria (grade 3 or worse) at 2.2% with a RR of 4.79 (95% CI: 2.71–8.46). The RR of developing nephrotic syndrome with chemotherapy containing bevacizumab (when compared with chemotherapy without bevacizumab) was 7.78 (ref. 16). Renal cell cancers tended to have an increased risk of proteinuria compared with other cancers.[16] Several of the trials reporting data on proteinuria from major cancer studies did so using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (Table 2). This classification has inherent limitations in interpretation and needs to be analyzed further for application in renal outcomes and assessment of proteinuria.

Information regarding proteinuria with newer generation of TKIs, many of which are orally active drugs instead of monoclonal antibodies, is limited. Sunitinib[17,18] and sorafenib[19] have been reported to cause proteinuria in case reports. Pazopanib has been more widely linked to the development of proteinuria. In a phase I trial involving 63 patients with advanced-stage refractory solid tumors, Hurwitz *et al.*[20] identified proteinuria with pazopanib in 5% of the patients

Table 2 | Grades of proteinuria and hypertension used for clinical trials

	Grade I	Grade II	Grade III	Grade IV	Grade V
Proteinuria	1+ on dipstick or 0.15–1.0 g/24 h	2+ to 3+ on dipstick or >1.0–3.5 g/24 h	4+ on dipstick or >3.5 g/24 h	Nephrotic syndrome	Death
Hypertension	Asymptomatic, transient (<24 h) increase by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously WNL; intervention not indicated	Recurrent or persistent (⩾24 h) or symptomatic increase by >20 mm Hg (diastolic) or to >150/100 mm Hg if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death

Abbreviation: WNL, within normal limits.
Common Terminology Criteria for Adverse Events (v 3.0) Grading of Proteinuria and Hypertension in Cancer Trials.[34]

and grade 3 or 4 proteinuria in 3% of all the patients. In a phase II study of pazopanib involving 225 patients with metastatic renal cell cancer, there was no mention of proteinuria as an adverse event. However, in this report, only adverse events occurring in greater than 10% of patients were reported.[21] In a phase III trial of pazopanib in patients with advanced renal cell cancer, 435 patients were enrolled and had an incidence of 9% proteinuria, with grade 3 or above proteinuria in <1% of the patients.[22] Cediranib, a recently developed potent VEGF inhibitor, currently in evaluation in phase III trials, has also been reported to cause proteinuria in phase II trials. In a phase II study of recurrent epithelial ovarian cancers, cediranib caused proteinuria in 30% of the patients within 2 weeks. However, none developed high-grade proteinuria.[23] These data reveal that it is possible that newer TKIs may have reduced incidence of development of proteinuria. However, they need to be viewed with caution because of heterogeneity in reporting this important adverse effect. At the very least, patients should undergo urine protein/creatinine ratio testing on a second morning void before and after receiving the drug. More long-term information is needed regarding their side effects.

Biopsy findings. Reports of renal biopsies among patients with proteinuria receiving TKIs are sparse. When reported, the most common causative agent was bevacizumab. Pathological findings have included 12 cases of TMA, two cases of collapsing glomerulopathy, and isolated reports of cryoglobulinemic and immune complex glomerulonephritis.[11] Details of the biopsy findings are listed in Table 3.

Thrombotic microangiopathy. TMA of the kidney is a localized manifestation of several severe systemic illnesses such as hypertensive emergency, scleroderma crisis, thrombotic thrombocytopenic purpura, and so on. Its pathogenesis has been primarily linked to endothelial damage. Inhibition of VEGF with TKIs leads to endothelial damage that results in local thrombosis as seen on biopsy. However, patients who developed TMA following exposure to TKI only manifested as renal dysfunction with low-grade proteinuria and did not have significant systemic findings of grave illnesses as mentioned earlier. Thus, there is a possibility of relative lack of correlation of findings of renal biopsy to systemic manifestations.

Renal biopsy is an invasive test and appropriately not done in all patients who develop proteinuria after exposure to TKIs. As such these findings may not be generalizable to all patients with proteinuria. However, as the severity of proteinuria correlates with patient outcomes, selected patients with high-grade proteinuria may be considered as candidates to have a lower threshold for kidney biopsy to better describe the renal manifestations of proteinuria with TKI.

Hypertension. Hypertension has been reported with the use of TKIs, including hypertensive crisis, which can be life threatening. In their meta-analysis, Zhu *et al.*[15] identified that low-dose bevacizumab was associated with hypertension, between 2.7 and 32% and 17.6 and 36% for the high-dose group. Grade III hypertension developed in 8.7% and 16% for low-dose and high-dose bevacizumab, respectively.[15] Bevacizumab was found to be associated with a significant increased risk of all grades of hypertension with RRs of 3.0 for low dose (95% CI: 2.2–4.2) and 7.5 for high dose (95% CI: 4.2–13.4). In a recent review, Ranpura *et al.*[24] evaluated more than 12,000 patients with various tumors across several studies specifically for high-grade hypertension with bevacizumab. They found an overall incidence of all-grade hypertension to be 23.6, with 7.9% being high grade (grade 3 or 4). The RR of developing high-grade hypertension was calculated to be around 5.28 (95% CI: 4.15–6.71). These findings were, however, dependent on the dose of bevacizumab and the type of tumor. A similar meta-analysis of sunitinib evaluating almost 5000 patients revealed an overall incidence of hypertension to be 8.6–29.6%. Summary incidence of high-grade hypertension was 6.8% (95% CI: 5.3–8.8%).[25] Higher incidence of hypertension was also noted in a phase II trial of the newer oral multi-TKI cediranib.[23] A total of 67% developed hypertension by day 3 of administration and 87% by the end of the study. More than 43% developed grade III hypertension. Only advanced age (>57 years) was identified as an independent predictor for the development of hypertension. Incidence of hypertension was uniformly around 30–40%, with a much lower incidence of grade 3 or higher hypertension (3–4% in phase II and III trials and up to 25% in phase I trial). Table 4 summarizes the current meta-analyses on the development of hypertension and proteinuria with TKI.

Mechanisms in the development of hypertension. The mechanism(s) of development of hypertension are far less

Table 3 | Renal biopsy findings reported in literature with use of TKIs

TKI	Malignancy	Biopsy findings
Bevacizumab,[6] sunitinib[18]	Hepatocellular cancer, bronchoalveolar carcinoma, small-cell lung cancer, metastatic ovarian cancer, malignant skin hidradenoma	Thrombotic microangiopathy with widening of the subendothelial space of glomerular capillaries, duplication of the glomerular basement membranes with cellular interposition, mesangiolysis, and extensive or focal effacement of foot processes. Focal or diffuse glomerular capillary thrombosis has been reported. In addition, modest mesangial deposition of IgA has also been seen
Bevacizumab[6]	Metastatic pancreatic cancer	Collapsing glomerulopathy with features of thrombotic microangiopathy
Bevacizumab[29]	Recurrent non-small-cell lung cancer	Cryoglobulinemic vasculitis[a]
Bevacizumab[30]	Pancreatic cancer, renal cell cancer	Immune complex-associated focal proliferative glomerulonephritis: thickened capillary wall segmental endocapillary hypercellularity with obliteration of capillary lumina segmental karyorrhexis. In addition mild segmental mesangial hypercellularity with slightly increased matrix was also noted. On immunofluorescence diffuse granular IgA deposits in the glomerular capillary walls and mesangial areas, κ- and λ-light chains, and mild fluorescence for IgG and IgM have been identified
Bevacizumab[31] Sorafenib[32]	Metastatic rectal leiomyosarcoma, metastatic renal cell cancer	Acute interstitial nephritis with polynuclear infiltration in some glomerular capillary walls in the setting of chronic glomerulopathy
Bevacizumab[33]	Metastatic small-cell cancer of lung	Crescentic glomerulonephritis: features of severe intimal fibrosis of arteries, mild hyalinosis of arterioles, and wide interstitial fibrosis associated with focal lymphocytic infiltration and tubular atrophy. Immunofluorescence showed mesangial granular IgM and C3 deposits and segmental staining for fibrinogen in the crescents

Abbreviations: Ig, immunoglobulin; TKI, tyrosine kinase inhibitor.
[a]Pathological findings not reported.

Table 4 | Meta-analyses evaluating proteinuria and hypertension with TKI

Study (reference)	TKI	*N*	No. of studies	Cancer type	Proteinuria (RR)	95% CI	HTN (RR)	95% CI
Zhu *et al.*[15]	Bevacizumab	1850	7	Several[a]	1.4 (low dose) 2.2 (high dose)	1.1–1.7 1.6–2.9	3 7.5	2.2–4.2 4.2–13.4
Ranpura *et al.*[24]	Bevacizumab	12,656	20	All cancers[b]	NA	NA	23.6	20.5–27.1
Wu *et al.*[16]	Bevacizumab	12,268	12	Several[c]	4.79	2.7–8.4	NA	NA
Zhu *et al.*[25]	Sunitinib	4999	13	Several[d]	NA	NA	21.6	18.7–24.8

Abbreviations: CI, confidence interval; CRC, colorectal cancer; HTN, hypertension; NA, not applicable; NSCLC, non-small-cell lung cancer; RCC, renal cell cancer; RR, relative risk; TKI, tyrosine kinase inhibitor.
[a]RCC, CRC, breast, NSCLC, and malignant mesothelioma.
[b]Underlying malignancies included CRC (seven studies), NSCLC (four studies), breast cancer (three studies), pancreatic cancer (three studies), RCC (three studies), and malignant mesothelioma (one study).
[c]CRC (six studies), NSCLC (two studies), breast cancer (three studies), pancreatic cancer (two studies), RCC (two studies), and malignant mesothelioma (one study).
[d]RCC, SCLC, gastrointestinal stromal tumor, gastric cancer, and urothelial carcinoma.

understood than proteinuria. Although inhibition of VEGF leads to significant proteinuria in animal models, the same has not been shown for development of hypertension. To further elucidate the mechanisms involved, Veronese *et al.* evaluated several biochemical and physiological parameters with the use of sorafenib. They measured plasma VEGF, total catecholamines, epinephrine, norepinephrine, endothelin I, urotensin II, renin, and aldosterone levels at baseline and again after 3 weeks of therapy among patients enrolled in a phase II randomized discontinuation clinical trial receiving sorafenib.[26] They also measured central aortic augmentation index and aortic pulse wave velocity as index of arterial stiffness. They found that none of the biochemical markers were significantly elevated to explain development of hypertension. However, there was a 30% increase in central aortic augmentation index and 9% increase in aortic pulse

wave velocity. These changes do not, however, explain how hypertension could develop in a matter of days. One of the leading explanations provided has been the nitric oxide (NO) generation hypothesis. It has been noted that VEGF exerts its angiogenic effects by enhancing the transcription of endothelial NO synthase.[27] Endothelial NO has vasodilatory properties, and inhibition of VEGF may lead to a decrease in NO and a resultant increase in the incidence of hypertension. The potential role of VEGF with regard to its vasodilatory properties was further explored in the Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis trial wherein 178 patients with stable exertional angina, unsuitable for standard revascularization, were randomized to receive either placebo or low- or high-dose recombinant human VEGF intracoronary, followed by intravenous administration on days 3, 6, and 9.[28] Significant decline in blood pressure was seen more so with the high-dose infusion of recombinant human VEGF. This appeared to have clinical significance too, as patients had a significant improvement in their angina scores, as well as quality of life. Unfortunately, these blood pressure-lowering effects were only transient and required intravenous infusions. Therapeutic implications for potential in treatment of uncontrolled hypertension exist but need to be balanced by the angiogenic effects, which may sometimes be undesirable. Further oral methods of delivery need to be devised for it to be a viable long-term treatment for hypertension.

Extrarenal side effects of TKI. Several unique extrarenal side effects of TKIs have been reported in the literature as opposed to other chemotherapeutic agents. These include, but are not limited to, cardiac ischemia or infarct, gastrointestinal perforation, thrombosis and thromboembolic events, reversible posterior leukoencephalopathy, and impaired wound healing. Various tubular disorders such as Fanconi syndrome, renal tubular acidosis, and nephrogenic diabetes insipidus may be seen with the use of chemotherapeutic agents. If identified in the clinical setting of TKI use, it may be difficult to distinguish from paraneoplastic effects of the underlying malignancy.

Management of proteinuria and hypertension

Proteinuria and hypertension are independent risk factors for adverse cardiovascular outcomes and progression of renal disease. With increasing survival in cancer patients, it is imperative that these side effects are recognized and managed appropriately. Evidence-based guidelines for management of proteinuria and hypertension with TKIs are lacking. For example, data on proteinuria have been collected using the NCI classification; this system uses definitions not commonly used by nephrologists. Further, several of the trials excluded patients with preexisting proteinuria and uncontrolled hypertension, limiting evaluation of probability of developing these side effects in such patient groups. However, current recommendations are to screen for the presence of proteinuria and hypertension before initiation and before each administration of cycled therapy or on a periodic basis when oral daily TKIs are used. Proteinuria may not be a reliable marker of TMA. For example, biopsy findings of severe TMA do not correlate well with proteinuria. In fact, several of those patients had only grade I or II proteinuria. However, the paucity of biopsy data makes this clinical correlation difficult and underscores the need for further studies. However, in practice, if there is persistent severe proteinuria, one must have a low threshold for renal biopsy, and if TMA is evident, consider risks and benefits for stopping TKIs and choosing alternate chemotherapeutic regimen. This may not be possible in situations in which TKIs are being used as a last resort for recurrent or advanced cancer. Additional discussion with patients regarding risks and benefits of continuation of these agents in such situations may be needed. As proteinuria may be frequently associated with hypertension, the use of angiotensin-converting enzyme inhibitors as a treatment option can be considered to lower proteinuria. Angiotensin-converting enzyme inhibitors also are the suggested first-line agents for patients who develop hypertension even in the absence of proteinuria. Although renin and angiotensin levels were not noted to be significantly elevated with VEGF inhibition, the favorable endothelial effects of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers make them an attractive first-line agent. Whether other agents such as diuretics, calcium

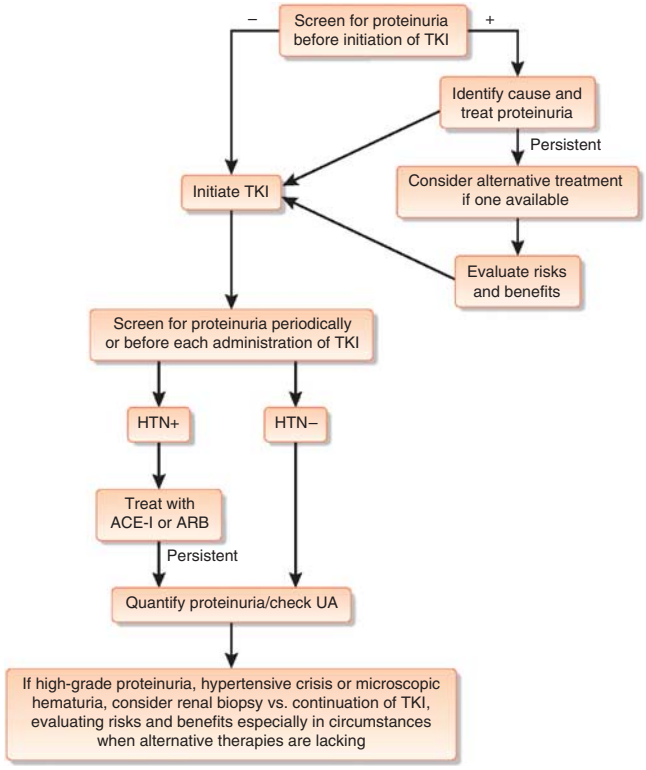

Figure 2 | An algorithm for screening and management of proteinuria and hypertension with tyrosine kinase inhibitors (TKIs). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HTN, hypertension; UA, urinalysis. See text for details.

channel blockers, or β-blockers provide similar or additional benefit is unknown and may be considered as viable alternatives. A suggested schema for management of hypertension and proteinuria with the use of TKIs is provided in Figure 2. This approach, however, needs to be confirmed for its efficacy in prospective trials.

CONCLUSIONS

TKIs are an effective antineoplastic treatment option for treatment of several advanced cancers with relatively good success. There has been a significant investment in further development of these drugs given their impressive therapeutic potential. We expect to see the use of these medications to be more widespread in the near future. Recognizing the side effects of hypertension and proteinuria is important to avoid unnecessary diagnostic testing.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. *N Engl J Med* 2005; **353**: 172–187.
2. Cook KM, Figg WD. Angiogenesis inhibitors: current strategies and future prospects. *CA Cancer J Clin* 2010; **60**: 222–243.
3. Kawachi H, Suzuki K, Miyauchi N *et al.* Slit diaphragm dysfunction in proteinuric states: identification of novel therapeutic targets for nephrotic syndrome. *Clin Exp Nephrol* 2009; **13**: 275–280.
4. Sugimoto H, Hamano Y, Charytan D *et al.* Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. *J Biol Chem* 2003; **278**: 12605–12608.
5. Eremina V, Sood M, Haigh J *et al.* Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. *J Clin Invest* 2003; **111**: 707–716.
6. Eremina V, Jefferson JA, Kowalewska J *et al.* VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008; **358**: 1129–1136.
7. Ganju RK, Munshi N, Nair BC *et al.* Human immunodeficiency virus tat modulates the Flk-1/KDR receptor, mitogen-activated protein kinases, and components of focal adhesion in Kaposi's sarcoma cells. *J Virol* 1998; **72**: 6131–6137.
8. Maynard SE, Min JY, Merchan J *et al.* Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003; **111**: 649–658.
9. Masuda Y, Shimizu A, Mori T *et al.* Vascular endothelial growth factor enhances glomerular capillary repair and accelerates resolution of experimentally induced glomerulonephritis. *Am J Pathol* 2001; **159**: 599–608.
10. Kim YG, Suga SI, Kang DH *et al.* Vascular endothelial growth factor accelerates renal recovery in experimental thrombotic microangiopathy. *Kidney Int* 2000; **58**: 2390–2399.
11. Izzedine H, Massard C, Spano JP *et al.* VEGF signalling inhibition-induced proteinuria: mechanisms, significance and management. *Eur J Cancer* 2010; **46**: 439–448.
12. Yang JC, Haworth L, Sherry RM *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Eng J Med* 2003; **349**: 427–434.
13. Hemmelgarn BR, Manns BJ, Lloyd A *et al.* Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010; **303**: 423–429.
14. Matsushita K, van der Velde M, Astor BC *et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073–2081.
15. Zhu X, Wu S, Dahut WL *et al.* Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007; **49**: 186–193.
16. Wu S, Kim C, Baer L *et al.* Bevacizumab increases risk for severe proteinuria in cancer patients. *J Am Soc Nephrol* 2010; **21**: 1381–1389.
17. Jhaveri KD, Flombaum CD, Kroog G *et al.* Nephrotoxicities associated with the use of tyrosine kinase inhibitors: a single-center experience and review of the literature. *Nephron Clin Pract* 2010; **117**: c312–c319.
18. Bollée G, Patey N, Cazajous G *et al.* Thrombotic microangiopathy secondary to VEGF pathway inhibition by sunitinib. *Nephrol Dial Transplant* 2009; **24**: 682–685.
19. Patel TV, Morgan JA, Demetri GD *et al.* A preeclampsia-like syndrome characterized by reversible hypertension and proteinuria induced by the multitargeted kinase inhibitors sunitinib and sorafenib. *J Natl Cancer Inst* 2008; **100**: 282–284.
20. Hurwitz HI, Dowlati A, Saini S *et al.* Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res* 2009; **15**: 4220–4227.
21. Hutson TE, Davis ID, Machiels JP *et al.* Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2010; **28**: 475–480.
22. Sternberg CN, Davis ID, Mardiak J *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; **28**: 1061–1068.
23. Robinson ES, Matulonis UA, Ivy P *et al.* Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. *Clin J Am Soc Nephrol* 2010; **5**: 477–483.
24. Ranpura V, Pulipati B, Chu D *et al.* Increased risk of high-grade hypertension with bevacizumab in cancer patients: a meta-analysis. *Am J Hypertens* 2010; **23**: 460–468.
25. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. *Acta Oncologica* 2009; **48**: 9–17.
26. Veronese ML, Mosenkis A, Flaherty KT *et al.* Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol* 2006; **24**: 1363–1369.
27. Hood JD, Meininger CJ, Ziche M *et al.* VEGF upregulates ecNOS message, protein, and NO production in human endothelial cells. *Am J Physiol* 1998; **274**: 1054–1058.
28. Henry TD, Annex BH, McKendall GR *et al.* The VIVA trial: vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. *Circulation* 2003; **107**: 1359–1365.
29. Johnson DH, Fehrenbacher L, Novotny WF *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; **22**: 2184–2191.
30. George BA, Zhou XJ, Toto R. Nephrotic syndrome after bevacizumab: case report and literature review. *Am J Kidney Dis* 2007; **49**: e23–e29.
31. Barakat RK, Singh N, Lal R *et al.* Interstitial nephritis secondary to bevacizumab treatment in metastatic leiomyosarcoma. *Ann Pharmacother* 2007; **41**: 707–710.
32. Izzedine H, Brocheriou I, Rixe O *et al.* Interstitial nephritis in a patient taking sorafenib. *Nephrol Dial Transplant* 2007; **22**: 2411.
33. Stylianou K, Lioudaki E, Papadimitraki E *et al.* Crescentic glomerulonephritis associated with vascular endothelial growth factor (VEGF) inhibitor and bisphosphonate administration. *Nephrol Dial Transplant* 2011; **26**: 1742–1745.
34. Cancer Therapy Evaluation Programme. *Common Terminology Criteria for Adverse Events (version 3.0; March 31, 2003)*. National Cancer Institute, National Institutes of Health: Rockville, MD. http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf (accessed 22 March 2010).